App. No. 10/526,858
Office Action Dated January 12, 2007

AMENDMENTS TO THE DRAWINGS

Please amend the drawings by deleting the reference to "Additive effect" in Fig. 1D (at the lower left corner of the graph), and replacing the reference with "Synergistic effect." This revision is supported, for instance, at page 17, line 26 to page 18, line 4. No new matter has been added. A --Replacement Sheet-- is attached herewith.

PAGE 4/14 * RCVD AT 6/12/2007 4:34:03 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-2/3 * DNIS:2738300 * CSID:612-455-3801 * DURATION (mm-ss):03-34

App. No. 10/526,858
Office Action Dated January 12, 2007

REMARKS

Reconsideration is respectfully requested in view of the above amendments and following remarks. Drawing sheet having Figs. 1A-D has been amended as discussed above. Claims 1-4 and 9 are canceled without prejudice or disclaimer. No new matter has been added. Claims 15-16, and 27 are pending.

Claims 1-4, 9, 15-16, and 27 have all been rejected under 35 U.S.C. 103(a) as being unpatentable over reference combinations including Hidaka et al. (US 5972976) in view of Goodman and Gilman, The Pharmacological Basis of therapeutics and Ragaz et al., The New England J. of Med. Applicants respectfully traverse the rejection to the extent it is maintained.

Claim 27 is directed to a method for treating a patient suffering from malignant tumor comprising administering a therapeutically effective amount of the compound of the formula (I), or a pharmaceutically acceptable salt thereof in combination with at least one other antitumor agent to the patient in need thereof. Claim 27 further requires, among other features, that the other antitumor agent is selected from the group consisting of cisplatin and carboplatin.

The claimed invention provides unexpected advantageous results in that an antitumor effect can be increased while toxicity of respective agents can be reduced. That is, the present invention can provide enhanced therapeutic effect while decreasing side effects.

The rejection contends that the disclosure relied upon is insufficient to show unexpected results, because the combined use of a compound 2 and cisplatin (CDDP) merely shows an added therapeutic effect resulting from increased dosages.

PAGE 8/14 * RCVD AT 6/12/2007 4:34:03 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-2/3 * DNIS:2738300 * CSID:612-455-3801 * DURATION (mm-ss):03-34

Applicants respectfully disagree and contend that the evidence shows the claimed invention does enjoy unexpected results.

Table 1 as well as the Figures in Applicants' disclosure show that the therapeutic method of the claimed invention provides unexpected results. Table 1 shows that the combined administration of compound 2 and cisplatin (CDDP) exerts superior effect over single administration of each agent even at a maximum tolerated dose for each agent. In Table 1, results are shown where compound 2 is administered alone at a maximum tolerated dose of 100 mg/kg, and where CDDP is administered alone at a maximum tolerated dose of 10 mg/kg. When compound 2 is administered alone at a maximum tolerated dose of 100 mg/kg, the maximum T/C % is 165% or 150%. When CDDP is administered alone at a maximum tolerated dose of 10 mg/kg, the maximum T/C % is 170%. In both instances of single administration, no survival is observed.

However, when both agents are administered, even when both agents are used at a moderate dose (i.e. 50 mg/kg of compound 2 and 5 mg/kg of CDDP), a T/C % is observed (240%) that is higher than either of the single administrations of each agent alone at their maximum tolerated doses. Thus, it is clear that combined administration of the agents gives a higher T/C % (Treated group/Control group %) even at significantly lower dosages than does single administration of each agent at a maximum tolerated dose. Furthermore, when both agents are administered at a maximum tolerated dose (i.e. 100 mg/kg of compound 2 and 10 mg/kg of CDDP), an even higher T/C % is observed (290%) and two animals among six survived on day 50, which is about 33% and which shows that combined administration enjoys an unexpected survival benefit. Such effect

PAGE 9/14 * RCVD AT 6/12/2007 4:34:03 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-2/3 * DNIS:2738300 * CSID:612-455-3801 * DURATION (mm-ss):03-34

is neither shown nor reasonably expected from the single administration of compound 2 or CDDP, even at a maximum tolerated dosage.

Moreover, sequential combined administration also shows unexpected results. When both agents compound 2 and CDDP are administered in sequential combined administration at a minimal dose (i.e. 25 mg/kg of compound 2 and 2.5 mg/kg of CDDP), a T/C % is observed (175 or 170%) that is at least the same as or higher than either of the single administrations of each agent alone at their maximum tolerated doses. Thus, it is clear that combined administration of the agents gives a higher T/C % (Treated group/Control group %) even at a minimal dose than does single administration of each agent at a maximum tolerated dose. Further, when the agents are administered in sequential combined administration, and where both agents are used at a maximum tolerated dose (i.e. 100 mg/kg of compound 2 and 10 mg/kg of CDDP), an even higher T/C % is observed (270 or >500%). Even further, the results show that two or five animals respectively, among six survived on day 50, which respectively is about 33% or 88%. Such results show that combined administration also enjoys a survival benefit that is neither shown nor reasonably expected from the single administration of compound 2 or CDDP, even at a maximum tolerated dosage. Thus, combination therapy as required by the claimed invention provides unexpected therapeutic effects, namely extended life, and irrespective of the manner of administration.

Applicants' originally disclosed Figures further support the position of unexpected results. Figures 2A and 2B show that that the combined administration of compound 3 and cisplatin (CDDP), and in either order, provides a superior effect over single administration. Figures 2A and 2B show effects of combined administration of

PAGE 10/14 * RCVD AT 6/12/2007 4:34:03 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-2/3 * DNIS:2738300 * CSID:612-455-3801 * DURATION (mm-ss):03-34

compound 3 and CDDP evaluated by analysis using Isobologram. (See descriptions at bottom of page 16 through page 18 of Applicants disclosure.) As described, the dose-response curve of each drug (single administration) is prepared, then D_A, D'_A, D''_A, D_B, D'_B, and D''_B are obtained and used to prepare Mode I, Mode II(A) and Mode II(B) in Isobologram. The vertical and horizontal axes of Figures 2A and 2B represent quotients obtained by dividing a concentration of the indicated agent added by IC_{50} value of said agent when administered alone. Each plot (•) in Figures 2A and 2B indicates the relative concentration of compound 3 and that of CDDP required to exert 50% growth inhibitory effect in combined administration, each relative concentration being calculated based on the concentration of each agent required to provide 50% growth inhibitory effect in single administration.

Moreover, Figure 1D shows that:

(1) when a plot enters in the region surrounded by Mode I (solid line) and Mode II (dotted line), that is, the dose required for IC_{50} in the combined administration is equivalent to the predictive dose, the two antitumor agents show additive effect.

(2) when a plot enters in the left lower region, that is, the dose in the combined administration is less than the predictive dose, the two antitumor agents show synergistic effect.

(3) when a plot enters in the right upper region, that is, the dose in the combined administration is more than the predictive dose, the effect is determined to be less than an additive effect (e.g. sub-additive).

PAGE 11/14 * RCVD AT 6/12/2007 4:34:03 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-2/3 * DNIS:2738300 * CSID:612-455-3801 * DURATION (mm-ss):03-34

For the Examiner's convenience, Applicants also respectfully submit Figures 2A and 2B as an Appendix, which further shows the distinction between where additive effects are observed (shaded portion), and where synergistic effects are shown (inner portion).

In view of the foregoing findings, Applicants submit that the present invention provides benefits that would have been unexpected to one of ordinary skill in the art. Thus, the claimed invention is not obvious over Hidaka et al and Goodman.

With respect to Ragaz, this reference is directed to radiotherapy. Applicants respectfully maintain that this reference is rendered moot as claims 10-12 were canceled. Therefore, the reference is not relevant.

For at least the foregoing reasons, claim 15-16, and 27 are patentable. The rejection is no longer applicable to claims 1-4 and 9, as these claims have been canceled. Applicants do not concede the correctness of the rejection as to these claims.

Favorable reconsideration and withdrawal of the rejection are respectfully requested.

A Notice of Allowance is respectfully solicited. Any questions or concerns regarding this communication can be directed to Applicants' representative listed below.

Respectfully submitted,

HAMRE, SCHUMANN, MUELLER & LARSON, P.C.
P.O. Box 2902-0902
Minneapolis, MN 55402-0902
(612) 455-3800

Dated: June 12, 2007

By: _____
Douglas P. Mueller
Reg. No. 30,300

PAGE 12/14 * RCVD AT 6/12/2007 4:34:03 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-2/3 * DNIS:2738300 * CSID:612-455-3801 * DURATION (mm-ss):03-34